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14. ABSTRACT

We propose to use a large, diverse, longitudinal study of middle aged and older Americans to identify social factors that help individuals preserve functional independence in basic and instrumental ADLs as long as possible, even in the context of declining memory or severe memory impairment. We focus on factors that are potentially modifiable and therefore have the greatest potential to inform decisions of people living with memory impairment, their families, physicians, military planners, and policy makers. We found strong associations between decreased cognitive functioning and incident ADL limitations. Physical activity may help to decrease the risk of functional impairment even among those with cognitive impairment, while smoking and depression may increase the risk of incident ADL limitations among those with cognitive impairments. This finding has critical importance for clinicians, patients, and family members of individuals with cognitive impairments or incipient dementia. By managing conventional risk factors, it may be possible to stave off dependencies, maximize quality of life, and minimize caregiver burden. This is especially important for older veterans and those with prior exposure to mild, moderate, or severe TBI, who are at elevated risk of memory loss and dementia.

15. SUBJECT TERMS
Cognitive impairment, Functional Limitations, Individual-level resilience factors

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INTRODUCTION

Memory losses are common among long-term survivors of traumatic brain injury (TBI) and TBI has been linked to increased risk of memory impairment and dementia. This is an important determinant of long-term well-being for military service men and women and their families, because of the elevated incidence of TBI in combat areas. Memory and cognitive impairments predict substantial losses in ability to independently manage daily activities; this loss of independence can be devastating to the individual and his or her family. To avoid dependence, we need to identify factors which preserve independence even in the face of memory and cognitive losses. While studies have examined predictors of institutionalization among those with dementia(*1*), factors like depression which predict institutionalization may be undertreated among those with dementia.(*2*) It is not known whether managing these risk factors among individuals with cognitive impairment is important because little research has been done on whether resources at personal and environmental levels can modify the translation of impairments caused by neurodegenerative diseases into functional disabilities. Current understanding of disability emphasizes that physical impairments in body functioning or structure do not necessarily induce functional disability because environmental, behavioral, and instrumental accommodations can foster continued independence.(*3*) Figure 1, an adaptation of the disablement process model by Verbrugge and Jette(*4*), demonstrates the process by which illness pathology and cognitive impairment may lead to functional limitations and disability. However, individual level modifiers like physical activity or not being depressed may also influence functional limitations and the individual's ability to use accommodations or coping strategies and may help promote functional independence even among individuals with memory loss or dementia. We propose to use data from the nationally representative Health and Retirement Study (HRS), a large, diverse, longitudinal study of middle aged and older Americans, to identify modifiable individual-, family- and community-level factors that help individuals preserve functional independence as long as possible even in the context of declining memory or cognitive impairment.

BODY

Tasks to be accomplished by 19 April 2013 as outlined in the statement of work:

1. Estimate the association between memory/cognitive losses and changes in functional independence in HRS cohort members (Q3 2012)
2. Test individual level resiliency factors as modifiers of the effects of memory on functional impairments in longitudinal models (Q3 2012 through Q1 2013)

We used data from individuals enrolled in the Health and Retirement Study. The sample included 4,922 Health and Retirement Study participants aged 65+ without limitations in activities of daily living (ADLs) at baseline. Participants were interviewed biennially up to 12 years. Cognitive status was assessed through a dementia probability score and a memory score, both of which were estimated from composites of direct and proxy assessments. Methods for calculating these scores have been described in detail elsewhere.(*5*) We divided the dementia probability score and memory score into four categories representing low, mild, moderate or high probability of developing dementia or of having memory impairments. Our outcome was reported difficulty in any of the five activities of daily living (getting across a room, dressing, bathing, eating, and getting in and out of bed) in the past 30 days. Possible response options were yes, no, or do not do, which was treated as missing in this analysis. We used the RAND version of the HRS data. We looked at each activity individually and also used the RAND variable for any activity limitation which captures incident limitations in any of the five activities of daily living. Hypothesized modifiers were self-reported physical activity, smoking, alcohol consumption, depression and income. Due to changes in the assessment of physical activity levels over time, physical activity was dichotomized as active versus inactive with active being defined as vigorous activity 3 or more times per week in 1998, 2000 and 2002, and as more than 1 time per week from 2004 onwards. The category of more than 1 time per week was the closest to the 3 or more times per week categorization available from 2004 onward. Alcohol consumption was dichotomized into moderate drinking versus non-moderate drinking. Moderate drinking was defined as consuming more than zero but fewer than two drinks per day. Drinks per day were calculated by dividing the number of drinks consumed on days the participant drinks by the number of days the participant reported drinking. Current smoking status was a binary variable (yes/no). An indicator variable for depression was constructed based on reporting 3 or more depressive symptoms on a modified 8-item Centers for Epidemiologic Studies-Depression (CES-D) scale in the past two weeks. This threshold has been shown to have high sensitivity (71%) and specificity (79%) for depression per the CIDI-SF. (*6*) We also constructed a time-updated indicator variable for low income using a cutpoint of $12,031 (based on the 25th percentile of the household-size adjusted income at baseline). Modifier information was assessed in the wave prior to outcome assessment.

Pooled logistic regression models were used to estimate the risk of incident activity limitations associated with dementia probability score categories. The relationship of the dementia probability categories with risk of ADL limitations was approximately linear, so the categories were treated as a linear variable. Participants were censored from analysis after last interview, onset of activity limitations, death or at first wave missing information on dementia probability. We used inverse probability weights (IPWs) to adjust for potential time-varying confounding. IPWs required one wave of "run-in" (see below), so our first "exposure" wave was in 2000 and our first "outcome" wave was in 2002. Those who reported ADL limitations in 1998 or 2000 were excluded from our analyses. Exposure and modifier information was always assessed one wave prior to the outcome wave.

Separate models were constructed examining dementia probability score and incident ADL limitations and memory score categories and incident ADL limitations. To assess whether any of our modifiers ameliorated or exacerbated the effects of dementia score on ADL limitations, two different approaches were used. First, we included an interaction term between dementia score category and each modifier (in separate models for each modifiers) to test

whether each modifier had different relative effects on ADL limitations depending on the participant's dementia score. Next to compare the absolute effects of each modifiers in participants with highest or lowest dementia score, we calculated the marginal probability of developing an activity limitation according to modifier status and dementia category. All analyses were performed using PROC SURVEYLOGISTIC in SAS 9.2 (SAS Institute, Cary, NC) with weights as described below.

To avoid introducing bias by adjusting for variables that may be affected by prior exposure and affect future exposure, inverse probability weights were used to adjust for time-varying confounders. Four different weights were constructed: for "treatment" (in this case the category of dementia score), for modifier status (separate weights were calculated for each modifier), for survival and for participation (not dropping out of the study). These weights were multiplied together to create a weight for each observation reflecting the inverse probability that the individual was alive and participated in the outcome wave; and had the dementia and modifiers values he or she actually had given his or her past dementia, modifier, and covariate history. We additionally included the survey weight for selection into the HRS sample. Weights were stabilized using previously described methods.(*7*) Additionally, the weights were truncated at the value of the 98th percentile to minimize skew and the influence of outliers.

Table 1 shows the characteristics of the 4,922 individuals included in our analyses by dementia probability category in 2000 (our first exposure wave). The percentage of individual who were physically active or currently consume alcohol and the mean household-size adjusted income was lower among those with higher dementia category. In contrast, the percentage of individuals with depression was lower among those with higher dementia category. Table 2 shows the distribution of participants in the four dementia categories and the number of outcome events by year.

As expected, higher dementia probability score category was associated with increased risk of incident ADL limitations with a per category OR of 1.65 (95% CI: 1.49-1.83). This implies individuals with highest dementia category (>75% probability of dementia) had 4.47 times the odds of onset of ADL limitations as individuals in the lowest dementia category (≤25% probability of dementia). We observed similar results for the association between memory score categories and any incident ADL limitation (OR=1.67; 95% CI: 1.45-1.92) as we did for dementia.

Table 3 shows the association between dementia probability score category and risk of incident ADL limitations, the association between each modifier and incident ADL limitations, and the interaction coefficient between dementia probability and each modifier. In these models, an interaction coefficient of 1 indicates the modifier has the same relative effect on ADL limitations regardless of dementia risk; if the interaction coefficient is less than 1, it indicates the modifier effect is lower (less harmful) among those with higher dementia risk.

For example, for the outcome of any ADL limitation, among the physically active, each unit increase in dementia score was associated with an OR of 1.82 (95% CI: 1.36-2.45). Low physical activity was associated with an increase in incident ADL limitations among those with the lowest dementia risk score (OR=1.51 (95% CI: 1.26-1.82). The interaction between physical activity and dementia risk was close to 1 and not significant (OR=0.86; 95% CI: 0.63-1.18), indicating that the relative harm of low physical activity was similar regardless of dementia category. We observed similar results for non-moderate drinking and current smoking. Non-moderate drinking and current smoking were associated with an increased risk of ADL limitations, but the relative harm of non-moderate drinking or current smoking was similar regardless of dementia category. Depression was also associated with an increased risk of ADL limitations and the interaction between depression and dementia risk suggested depression may be less harmful among the cognitively impaired (OR=0.73; 95% CI: 0.57-0.93). Low income was not associated with an increased risk of ADL limitations (OR=0.95; 95% CI: 0.74-1.23) and the interaction between low income and dementia was also closer to the null.

Table 4 shows the association between memory score category and risk of incident ADL limitations in models including an interaction term between memory category and each modifier

in separate models. Worse (higher) memory score is associated with higher risk of incident ADL limitations. The results for memory and physical activity, smoking, or depression were similar to those seen for dementia. Unlike the results for dementia, non-moderate drinking was not associated with an increased risk of ADL limitations in our memory models. The interaction term between drinking and memory category was not statistically significant, but it was above one which may indicate non-moderate drinking is more harmful among those with high dementia risk. Finally, low income was associated with an increased risk of ADL limitations, but the relative harm of low income is similar regardless of dementia category.

To further explore the joint effects of dementia category and modifier status on incident ADL limitations, we calculated the marginal probability of developing any incident ADL limitations for each combination of dementia category and modifier status. For clarity, we contrast probability of incident ADL limitations in those with the lowest dementia category (0-0.25) and those with the highest dementia category (0.75-1) (Figure 1). For example, individuals in the lowest dementia category who are physically inactivity have a 11.5% probability of developing any incident ADL limitation. If a similar person is physically active, the probability of developing an ADL limitation is only 8.2%, thus physical activity reduces the probability of incident ADL limitations by 3.3 percentage points among those with low dementia probability. Physically inactive individuals with the highest high dementia scores have a 33.5% chance of developing an ADL limitation, but physically active individuals with high dementia probability have only a 26.1% chance of developing any incident ADL limitation. Physical activity reduces the probability of incident ADL limitations by 7.4 percentage points among individuals who are in the highest dementia probability category. Therefore, the absolute effect of physical activity is larger among those with higher dementia probability. Similar comparisons can be made for the other modifiers. Current smoking, non-moderate drinking and depression have a larger adverse effect on the probability of developing incident ADL limitations among those with high dementia probability than among those with low dementia probability. In contrast low income seems to have similar effects among for low and high dementia probability.

Figure 2 shows the marginal probabilities of developing any incident ADL limitation by memory category and modifier status. Again, we show results contrasting the worst and best memory score to simplify the presentation. Similar to the findings for dementia probability, physical activity results in a greater reduction in the probability of developing any ADL limitation in the context of poor memory score (from 29.1% to 22.3% for a reduction of 6.8 percentage points) than good memory score (from 8.3% to 5.9% for a reduction of 2.4 percentage points). Current smoking, being depressed, having low income and non-moderate drinking resulted in a greater increase in probability of developing ADL limitations among individuals with poor memory score than good memory score.

In addition to containing data on ADL limitations, the HRS cohort also assessed limitations in Instrumental Activities of Daily Living (IADLs). IADLs are often considered to be more cognitively demanding than ADLs. (*8*) Because of this, we thought the impact of our individual level modifiers may be different for ADLs versus IADLs. Additionally since there are many ways of analyzing functional outcomes data, we explored using a different analysis technique to analyze our IADL data. We have performed a second set of analyses using limitations in IADLs as our outcome and are drafting a separate manuscript to present these results. Our methods and results are outlined below.

Similar to the ADL analyses, our exposures were the four categories of dementia probability and the four categories of memory impairment. These categories were treated as linear variables. We used the same modifiers as those used in our ADL analyses (physical activity, smoking, alcohol consumption, depression and income). Our exposure and modifier status was also assessed in the wave prior to our outcome assessment.

For our outcome, we used limitations in the past 30 days in IADLs. The IADLs assessed in HRS were using a telephone, taking medication, handling money, shopping and preparing meals. Possible response options were yes, no, or do not do, which was treated as missing in

this analysis.

While pooled logistic regression with inverse probability weighting is the most appropriate technique for analyzing binary outcome events, it cannot handle count data. This is potentially a limitation since it is possible that an individual may have multiple IADL limitations. In this scenario the outcome would be a "count" instead of a binary outcome. To analyze count data, we must use Poisson regression. To correct for overdispersion and clustering, we will use sandwich variance estimators. (*9*) Each year, we counted the total number of IADL limitations reported by an individual and used this count as our outcome variable. First we tested the association between cognitive status and incident IADL limitations. Next, we assessed multiplicative interactions of each modifier with dementia in predicting IADL limitations.

Table 5 shows the distribution of participants in the four dementia categories, the number of people reporting IADL limitations and the mean number of IADL limitations reported by year.

As expected, higher dementia probability score category and higher memory score category were associated with increased risk of incident IADL limitations (relative risk=1.79, 95% CI: 1.72-1.87 and relative risk=2.23, 95% CI: 2.10-2.37 respectively).

Table 6 shows the association between dementia probability score category and risk of incident IADL limitations, the association between each modifier and incident IADL limitations, and the interaction coefficient between dementia probability and each modifier. In these models, if the interaction coefficient is 1, it indicates that modifier has the same relative effect on IADL limitations regardless of dementia risk; if the interaction coefficient is less than 1, it indicates the modifier effect is lower (less harmful) among those with higher dementia risk. We observed significant interactions between dementia probability score category and lack of physical activity, non-moderate alcohol consumption, depression and low income. All of the interaction terms were below one which indicates that the effect of the modifier is less harmful among those with higher dementia risk. This may indicate that for incident IADL limitations, cognitive status is a stronger predictor of functional limitations and unhealthy behaviors (like lack of physical activity) may not have as much of an impact in those with cognitive impairments as they would among those who are not cognitively impaired. Similar results were seen when using memory categories as our measure of cognitive status (Table 7).

Since we found evidence that our modifiers modify the association between cognitive function and IADL limitations, we performed analyses examining the association between cognitive function and IADL limitations stratified by modifier status. Table 8 shows the association between dementia probability score category and risk of incident IADL limitations stratified by risk factor status. In general, the impact of dementia probability status was stronger for those without the risk factor than for those with the risk factor. For example, among the physically active, higher dementia probability score category was associated with increased risk of incident ADL limitations with a per category relative risk of 2.03 (95% CI: 1.71-2.41). Among the physically inactive, higher dementia probability score category was associated with increased risk of incident ADL limitations with a per category relative risk of 1.76 (95% CI: 1.69-1.83). Similar results were seen when memory categories were used as our measure of functional status (Table 9).

Our next step is to draft a manuscript presenting the results of these IADL analyses.

Tasks to be in progress by 19 April 2013 as outlined in the statement of work:

1. Link family level variables and test family level resiliency factors as modifiers of the effects of memory on functional impairments (Q1 2013 through Q3 2013)

Due to delays in hiring the post-doctoral researcher and research assistant for this project, we have not yet begun work on this task. We anticipate that this work will begin in June.

KEY RESEARCH ACCOMPLISHMENTS

- Hired doctoral level programmer/post-doctoral fellow and a research assistant to implement statistical programming and other project work.
- Developed inverse probability weighting models to statistically account for selective survival and dropout.
- Completed statistical programming, specified core statistical models and derived preliminary estimates of the association between cognitive loss as measured by a dementia probability score and changes in functional independence as measured by six Activities of Daily Living (ADL) in Health and Retirement Survey (HRS) cohort members.
- Tested individual level resiliency factors as modifiers of the effects of cognitive impairment on ADL limitations using pooled logistic regression and inverse probability weighting.
- Drafted manuscript for cognitive impairment, individual-level modifiers and incident ADL limitations.
- Submitted an abstract to the Society of Epidemiological Research Annual Meeting
- Tested individual level resiliency factors as modifiers of the effects of cognitive impairment on IADL limitations using Poisson regression with sandwich variance estimators.

REPORTABLE OUTCOMES

- Drafted manuscript for cognitive impairment, individual-level modifiers and incident ADL limitations; will submit manuscript to *Neurology* by June 2013
- Abstract entitled: “Do behavioral factors prevent disability among cognitively impaired adults? An inverse probability weighted analysis” to be presented as a poster at the Society of Epidemiologic Research Annual Meeting in Boston June 19-21, 2013

CONCLUSION

We found strong associations between decreased cognitive functioning and incident ADL limitations. Physical activity may help to decrease the risk of functional impairment even among those with cognitive impairment, while smoking and depression may increase the risk of incident ADL limitations among those with cognitive impairments. This finding has critical importance for clinicians, patients, and family members of individuals with cognitive impairments or incipient dementia. By managing conventional risk factors, it may be possible to stave off dependencies, maximize quality of life, and minimize caregiver burden.

Disseminating these results is particularly important because conventional risk factors for ADL limitations like depression are often undertreated among those with cognitive impairment.(*2*) Even traditional vascular risk factors like high blood pressure, dyslipidemia, diabetes mellitus, smoking and atherosclerotic disease may be untreated in those with cognitive impairment. A study of patients with Alzheimer's disease without cerebrovascular disease but with at least one vascular risk factor found that 25.7% of patients had no vascular risk factors treated and 42.5% had only some risk factor treated.(*10*) However, maintaining healthy risk factor profiles may help individuals with incipient dementia to maintain functional independence, and thereby lower their risk for institutionalization and decrease care-giver burden.

In addition to examining the association between cognitive function, individual level modifiers and ADLs, it is also important to examine how individual level modifiers may impact the association between cognitive function and IADLs. Since IADLs are considered to have a stronger cognitive component than ADLs, the modifiers may have different impacts the association between cognitive function and IADLs. When examining IADLs, we observed a strong association between decreased cognitive functioning and incident IADL limitations. However, unlike our results for ADLs, we observed strong interactions between our modifiers and cognitive functioning. This may indicate that for incident IADL limitations, cognitive status is a stronger predictor of functional limitations and unhealthy behaviors (like lack of physical activity) may not have as much of an impact in those with cognitive impairments as they would among those who are not cognitively impaired. However, managing unhealthy behaviors is still important given their impact on ADL limitations.

While the present report describes the impact of individual-level modifiers on the association between cognitive impairment and functional limitations, there are many other family-level and neighborhood-level factors that have not yet been explored. It is important to explore these factors because they may offer new ways of breaking the link between cognitive impairments and functional limitations. The findings have the potential to substantially improve the quality of life of adults with memory impairments, reduce caregiving demands for family members, and delay institutionalization. This is especially important for older veterans and those with prior exposure to mild, moderate, or severe TBI, who are at elevated risk of memory loss and dementia. As the number of warfighters surviving TBI or other causes of cognitive impairment grows, it is crucial to identify the resources and tools that provide the greatest benefit to those individuals. Findings from this research can help provide guidance to individuals and families as well as clinicians, military planners, and policy makers.

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APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, study questionnaires, and surveys, etc.

Abstract for Society of Epidemiology Annual Conference in Boston, MA June 18-21, 2013

Do behavioral factors prevent functional disability among cognitively impaired adults? An inverse probability weighted analysis.

*P. M. Rist, B. D. Capistrant, Q. Wu, and M. M. Glymour (Harvard School of Public Health, Boston, MA 02115)

Abstract Body

Cognitive impairment predicts losses in the ability to independently manage activities of daily living (ADLs) but does not affect everyone equally. We followed 7,350 Health and Retirement Study participants aged 65+ and without activity limitations in 1998 biennially for 12 years to identify factors that preserve independence even in the context of cognitive losses. Hypothesized modifiers included physical activity and alcohol consumption. Dementia probability score, a measure of cognitive impairment, was divided into four categories with higher categories representing increased dementia probability. Dementia categories and modifier status were assessed one wave prior to activity assessment. We tested multiplicative interaction terms between each modifier and dementia category in pooled logistic regression models using inverse probability weights to adjust for time-varying confounders and attrition. Increasing dementia category predicted increased risk of ADL limitations (odds ratio (OR)=1.50; 95% CI: 1.39-1.62). Past wave physical activity was protective against incident ADL limitations (OR=0.59; 95%CI: 0.42-0.83) while past wave alcohol consumption had little effect (OR=0.93; 95% CI: 0.73, 1.18). Interaction terms between physical activity or alcohol consumption and dementia probability score were not significant on a multiplicative scale (p-values=0.72 and 0.59, respectively). For people with lowest dementia scores, physical activity reduced the probability of incident ADL limitations by 3 percentage points (0.13 to 0.10), but for people with highest dementia scores, physical activity reduced the probability of incident ADL limitations by 7 percentage points (0.35 to 0.28). In contrast, alcohol consumption resulted in a 1 percentage point increase in the probability of incident ADL limitations for low and high dementia scores. These results suggest physical activity may reduce the risk of activity limitations after onset of cognitive impairment.

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SUPPORTING DATA: All figures and/or tables shall include legends and be clearly marked with figure/table numbers.

Table 1. Baseline characteristics of those included in the analysis of dementia probability category and any incident ADL limitation by dementia probability category at baseline.

	Dementia Probability Category			
	0-0.25 (N=4,299)	0.25-0.50 (N=119)	0.50-0.75 (N=54)	0.75-1 (N=93)
Age (mean, std)	72.4 (5.6)	80.0 (6.8)	81.2 (6.0)	80.6 (6.7)
Gender (% male)	43.7	41.8	29.2	22.7
Race (% black)	9.1	19.9	15.4	24.0
Southern birthplace (%)	12.7	20.6	15.4	2.6
Years of education (mean, std)	12.6 (2.8)	10.8 (3.5)	9.9 (3.4)	9.9 (3.9)
Mother had ≥8 years of education (%)	53.0	45.9	36.9	33.3
Father had ≥8 years of education (%)	45.5	41.1	30.8	33.3
Height in meters (mean, std)	1.7 (0.1)	1.7 (0.1)	1.6 (0.1)	1.6 (0.1)
Marital status				
Married (%)	65.5	48.0	40.0	41.3
Divorced/separated (%)	6.3	5.5	9.2	5.3
Widowed (%)	24.7	43.2	49.2	52.0
Never married (%)	3.5	3.4	1.5	1.3
Not physically active (%)	51.3	63.7	69.2	84.0
Non-moderate drinking (%)	49.5	32.2	27.7	14.7
Current smoking (%)	8.9	10.3	1.5	4.0
Current depression (%)	9.3	19.2	13.9	18.7
Low household-size adjusted income (%)	18.4	39.0	50.8	50.7
Body mass index (mean, std)	26.1 (4.2)	25.4 (4.0)	24.2 (4.4)	24.4 (4.0)
Number of comorbidities (mean, std)	1.5 (1.2)	1.6 (1.1)	1.6 (1.3)	1.4 (1.2)

Table 2. Distribution of dementia probably score and number of incident any ADL limitations by year.

	Year					
Dementia Probability Category	2002	2004	2006	2008	2010	Any Incident ADL Limitation (n, %)
0-0.25 (n, %)	4203 (95.8%)	3407 (95.1%)	2707 (94.3%)	2156 (94.6%)	1616 (93.8%)	1349 (82.9%)
0.25-.50 (n, %)	112 (2.6%)	97 (2.7%)	87 (3.0%)	74 (3.2%)	62 (3.6%)	110 (6.8%)
0.5-0.75 (n, %)	39 (0.9%)	49 (1.4%)	37 (1.3%)	33 (1.4%)	27 (1.6%)	72 (4.4%)
0.75-1 (n, %)	32 (0.7%)	31 (0.9%)	41 (1.4%)	17 (0.7%)	17 (1.0%)	96 (5.9)
Any Incident ADL limitation (n)	536	390	378	298	259	1627

Note: Percentages may not add to 100% due to rounding.

Table 3. Association between dementia category and incident ADL limitations including interactions between dementia category and individual health factors.

	Any ADL Limitation			Walking			Dressing			Eating			Getting In/Out of Bed			Bathing		
	OR	95%	CI	OR	95%	CI	OR	95%	CI	OR	95%	CI	OR	95%	CI	OR	95%	CI
Physical Activity																		
Dementia Category	1.82	1.36	2.45	1.57	1.16	2.13	2.24	1.69	2.96	2.62	1.93	3.56	1.78	1.32	2.39	2.73	2.09	3.56
Dementia *No Physical activity	0.86	0.63	1.18	0.97	0.71	1.33	0.71	0.53	0.96	0.68	0.49	0.94	0.90	0.66	1.23	0.64	0.48	0.84
No Physical Activity	1.51	1.26	1.82	1.51	1.14	2.00	1.70	1.35	2.13	1.95	1.36	2.79	1.76	1.30	2.38	2.25	1.71	2.95
Drinking																		
Dementia Category	1.40	0.96	2.04	1.61	1.07	2.41	1.38	0.87	2.17	1.96	1.36	2.82	1.50	0.98	2.30	1.90	1.36	2.66
Dementia*Non-moderate drinking	1.12	0.76	1.66	0.95	0.62	1.45	1.25	0.79	1.98	0.90	0.62	1.32	1.05	0.68	1.62	0.90	0.63	1.29
Non-moderate Drinking	1.24	0.95	1.62	1.50	1.06	2.13	1.23	0.90	1.68	1.15	0.75	1.77	1.43	0.95	2.14	1.42	1.00	2.01
Smoking																		
Dementia Category	1.68	1.51	1.86	1.59	1.43	1.77	1.72	1.54	1.92	1.81	1.60	2.05	1.64	1.45	1.85	1.91	1.73	2.12
Dementia Category*Smoking	0.93	0.37	2.36	0.83	0.37	1.87	0.60	0.29	1.22	0.33	0.16	0.69	0.68	0.36	1.25	0.48	0.20	1.15
Smoking	1.62	0.94	2.78	1.37	0.68	2.73	1.27	0.67	2.41	2.52	1.22	5.22	2.01	0.96	4.25	2.18	1.21	3.95
Depression																		
Dementia Category	1.71	1.51	1.93	1.62	1.44	1.84	1.78	1.57	2.01	2.01	1.75	2.30	1.67	1.48	1.89	1.95	1.73	2.19
Dementia*Depression	0.73	0.57	0.93	0.90	0.66	1.22	0.79	0.63	1.00	0.75	0.56	1.01	1.05	0.78	1.42	0.90	0.68	1.20
Depression	1.59	1.26	2.01	1.69	1.31	2.18	1.53	1.20	1.94	2.64	1.89	3.68	1.53	1.14	2.06	1.46	1.14	1.88
Income																		
Dementia category	1.58	1.37	1.82	1.75	1.51	2.03	1.89	1.63	2.19	2.12	1.76	2.56	1.96	1.66	2.32	2.12	1.83	2.45
Dementia*Low Income	1.24	0.91	1.70	0.76	0.56	1.03	0.91	0.71	1.17	0.92	0.70	1.22	1.02	0.78	1.34	1.16	0.87	1.54
Low Income	0.95	0.74	1.23	1.27	0.94	1.72	0.92	0.71	1.20	1.33	0.89	1.99	1.04	0.73	1.47	0.90	0.67	1.21

List of abbreviations: ADL = activities of daily living; OR = odds ratio; CI = confidence interval

ORs show the association between dementia probability category and risk of incident ADL limitations in models including an interaction term between dementia category and each modifier. Physical inactivity and depression were associated with increased risk of incident

activity limitations. Non-moderate drinking and smoking were both associated with a non-significant increase in the risk of incident ADL limitations. Most of the interactions terms were close to the null and not statistically significant, indicating that the modifier terms have similar relative effects regardless of dementia risk.

Table 4. Association between memory score category and incident ADL limitations including interactions between memory score and individual health factors.

	Any ADL Limitation			Walking			Dressing			Eating			Getting In/Out of Bed			Bathing		
	OR	95%	CI	OR	95%	CI	OR	95%	CI	OR	95%	CI	OR	95%	CI	OR	95%	CI
Physical Activity																		
Memory Category	1.83	1.35	2.48	2.03	1.48	2.78	2.66	1.83	3.89	3.59	2.30	5.60	2.02	1.30	3.14	3.24	2.16	4.87
Memory *No Physical activity	0.90	0.65	1.23	0.85	0.60	1.21	0.71	0.48	1.04	0.67	0.42	1.05	1.04	0.65	1.68	0.50	0.33	0.76
No Physical Activity	1.60	1.14	2.25	1.64	1.10	2.46	2.31	1.51	3.55	3.15	1.74	5.70	1.52	0.86	2.72	3.86	2.30	6.47
Drinking																		
Memory Category	0.94	0.58	1.54	1.62	0.96	2.74	1.02	0.55	1.89	2.19	1.12	4.30	1.79	0.95	3.38	1.41	0.77	2.58
Memory*Non-moderate Drinking	1.40	0.84	2.33	1.12	0.64	1.95	1.82	0.98	3.38	0.94	0.46	1.90	1.18	0.63	2.21	1.20	0.65	2.24
Non-moderate Drinking	0.93	0.55	1.55	1.41	0.70	2.85	0.69	0.36	1.35	1.07	0.39	2.97	1.30	0.59	2.89	1.20	0.57	2.52
Smoking																		
Memory Category	1.78	1.53	2.07	1.75	1.47	2.09	2.08	1.72	2.52	2.25	1.82	2.78	2.06	1.66	2.55	1.94	1.63	2.30
Memory Category*Smoking	0.67	0.28	1.63	0.33	0.14	0.75	0.32	0.13	0.78	0.27	0.11	0.71	0.29	0.11	0.78	0.38	0.18	0.78
Smoking	2.19	1.05	4.56	3.40	1.46	7.89	3.10	1.33	7.23	4.54	1.51	13.62	4.14	1.52	11.23	3.80	1.65	8.74
Depression																		
Memory Category	1.69	1.42	2.01	1.99	1.64	2.40	1.98	1.59	2.46	2.90	2.31	3.63	2.21	1.74	2.81	2.13	1.72	2.63
Memory*Depression	0.91	0.65	1.27	0.74	0.49	1.11	0.94	0.60	1.47	0.61	0.39	0.93	0.86	0.53	1.38	0.74	0.50	1.07
Depression	1.64	1.09	2.46	2.12	1.28	3.52	1.50	0.81	2.77	3.92	2.16	7.11	2.02	1.02	4.00	1.83	1.11	3.00
Income																		
Memory category	1.68	1.44	1.95	2.14	1.79	2.56	1.82	1.52	2.18	2.48	1.95	3.16	2.13	1.72	2.64	2.03	1.69	2.43
Memory*Low Income	0.96	0.75	1.22	0.57	0.45	0.73	1.15	0.87	1.52	0.84	0.63	1.11	0.92	0.68	1.24	0.82	0.63	1.05
Low Income	1.40	1.04	1.88	2.78	1.99	3.87	1.25	0.86	1.84	1.98	1.30	3.03	1.52	1.01	2.28	1.76	1.24	2.50

List of abbreviations: ADL = activities of daily living; OR = odds ratio; CI = confidence interval

Brief explanation of Table 4: Table 4 shows the association between memory score category and risk of incident ADL limitations after including an interaction term between memory category and each modifier in separate models. In all models increasing memory score was associated with increased risk of incident ADL limitations. Physical inactivity, smoking,

depression and low income were also associated with an increased risk of incident ADL limitations. Similar to the dementia score results, most of the interaction terms were not statistically significant.

Table 5. Distribution of dementia probably score and total number of incident IADL limitations by year.

Dementia Probability Category	Year					Number of people reporting IADL Limitations (n)	Mean number of limitations reported (n, std)
	2002	2004	2006	2008	2010		
0-0.25 (n, %)	4963 (95.1)	4037 (95.1)	3212 (94.3)	2560 (93.7)	1978 (93.1)	1665	0.17 (0.64)
0.25-.50 (n, %)	150 (2.9)	112 (2.6)	108 (3.2)	107 (3.9)	87 (4.1)	171	0.73 (1.39)
0.5-0.75 (n, %)	69 (1.3)	56 (1.3)	50 (1.5)	43 (1.6)	39 (1.8)	125	1.23 (1.67)
0.75-1 (n, %)	37 (0.7)	40 (0.9)	36 (1.1)	22 (0.8)	20 (0.9)	92	1.82 (1.95)
Number of people reporting IADL Limitations (n)	524	512	400	290	327	2053	
Mean number of limitations reported (n, std)	0.19 (0.70)	0.22 (0.73)	0.22 (0.75)	0.20 (0.72)	0.33 (0.96)		0.22 (0.76)

List of abbreviations: IADL = instrumental activities of daily living; std = standard deviation

Table 6. Association between dementia score category and incident IADL limitations including interactions between dementia score and individual health factors.

	OR	95% CI	
Physical Activity			
Dementia Category	2.28	2.07	2.51
Dementia*No Physical activity	0.76	0.70	0.83
No physical Activity	1.86	1.64	2.10
Drinking			
Dementia Category	2.00	1.85	2.16
Dementia*Non-moderate Drinking	0.88	0.82	0.95
Non-moderate Drinking	1.52	1.34	1.71
Smoking			
Dementia Category	1.79	1.72	1.87
Dementia*Smoking	0.97	0.86	1.08
Smoking	0.90	0.73	1.12
Depression			
Dementia Category	1.88	1.80	1.96
Dementia*Depression	0.77	0.72	0.82
Depression	1.69	1.51	1.88
Income			
Dementia category	1.92	1.84	2.01
Dementia*Low Income	0.80	0.75	0.85
Low Income	1.40	1.24	1.57

List of abbreviations: IADL = instrumental activities of daily living; OR = odds ratio; CI = confidence interval

Brief explanation of Table 6: Table 6 shows the association between dementia score category and risk of incident IADL limitations after including an interaction term between dementia category and each modifier in separate models. In all models increasing dementia score was associated with increased risk of incident IADL limitations. Physical inactivity, non-moderate drinking, depression and low income were also associated with an increased risk of incident IADL limitations. Most of the interaction terms between our modifiers and dementia score categories were statistically significant.

Table 7. Association between memory score category and incident IADL limitations including interactions between memory score and individual health factors.

	OR	95% CI	
Physical Activity			
Memory Category	2.91	2.55	3.32
Memory*No Physical activity	0.74	0.65	0.84
No physical Activity	2.32	1.92	2.80
Drinking			
Memory Category	2.54	2.28	2.84
Memory*Non-moderate Drinking	0.85	0.77	0.95
Non-moderate Drinking	1.69	1.41	2.02
Smoking			
Memory Category	2.24	2.11	2.38
Memory*Smoking	0.95	0.81	1.11
Smoking	1.00	0.75	1.34
Depression			
Memory Category	2.37	2.22	2.51
Memory*Depression	0.71	0.65	0.79
Depression	2.15	1.83	2.52
Income			
Memory category	2.41	2.26	2.57
Memory*Low Income	0.76	0.70	0.83
Low Income	1.68	1.42	1.99

List of abbreviations: IADL = instrumental activities of daily living; OR = odds ratio; CI = confidence interval

Brief explanation of Table 7: Table 7 shows the association between memory score category and risk of incident IADL limitations after including an interaction term between memory category and each modifier in separate models. In all models increasing memory score was associated with increased risk of incident IADL limitations. Physical inactivity, non-moderate drinking, depression and low income were also associated with an increased risk of incident IADL limitations. Most of the interaction terms between our modifiers and memory score categories were statistically significant.

Table 8. Association between dementia score category and incident IADL limitations stratified by levels of the individual health factors.

	OR	95% CI	
Physical Activity			
Active	2.03	1.71	2.41
Not Active	1.76	1.69	1.83
Drinking			
Moderate drinker	1.84	1.61	2.09
Non-moderate drinker	1.78	1.70	1.86
Smoking			
Non-smoker	1.79	1.72	1.87
Smoker	1.63	1.38	1.93
Depression			
Not depressed	1.87	1.78	1.96
Depressed	1.49	1.37	1.61
Income			
Higher income	1.89	1.80	1.99
Low Income	1.59	1.48	1.69

List of abbreviations: IADL = instrumental activities of daily living; OR = odds ratio; CI = confidence interval

Brief explanation of Table 8: Table 8 shows the estimated associations between dementia score and incident IADLs stratified by risk factor status. The effect of dementia score is usually stronger among those without the risk factor (ie, those who are active, moderate drinkers, non-smokers, not depressed or have higher income).

Table 9. Association between memory score category and incident IADL limitations stratified by levels of the individual health factors.

	OR	95% CI	
Physical Activity			
Active	2.81	2.29	3.44
Not Active	2.16	2.03	2.30
Drinking			
Moderate drinker	2.34	1.97	2.78
Non-moderate drinker	2.18	2.05	2.32
Smoking			
Non-smoker	2.24	2.10	2.38
Smoker	1.93	1.51	2.46
Depression			
Not depressed	2.35	2.20	2.51
Depressed	1.71	1.51	1.93
Income			
Higher income	2.36	2.19	2.54
Low Income	1.91	1.73	2.11

List of abbreviations: IADL = instrumental activities of daily living; OR = odds ratio; CI = confidence interval

Brief explanation of Table 9: Table 9 shows the estimated associations between memory score and incident IADLs stratified by risk factor status. The effect of memory score is usually stronger among those without the risk factor (ie, those who are active, moderate drinkers, non-smokers, not depressed or have higher income).

Figure 1. Influence of individual-level health modifiers and cognitive impairment on the disablement process.

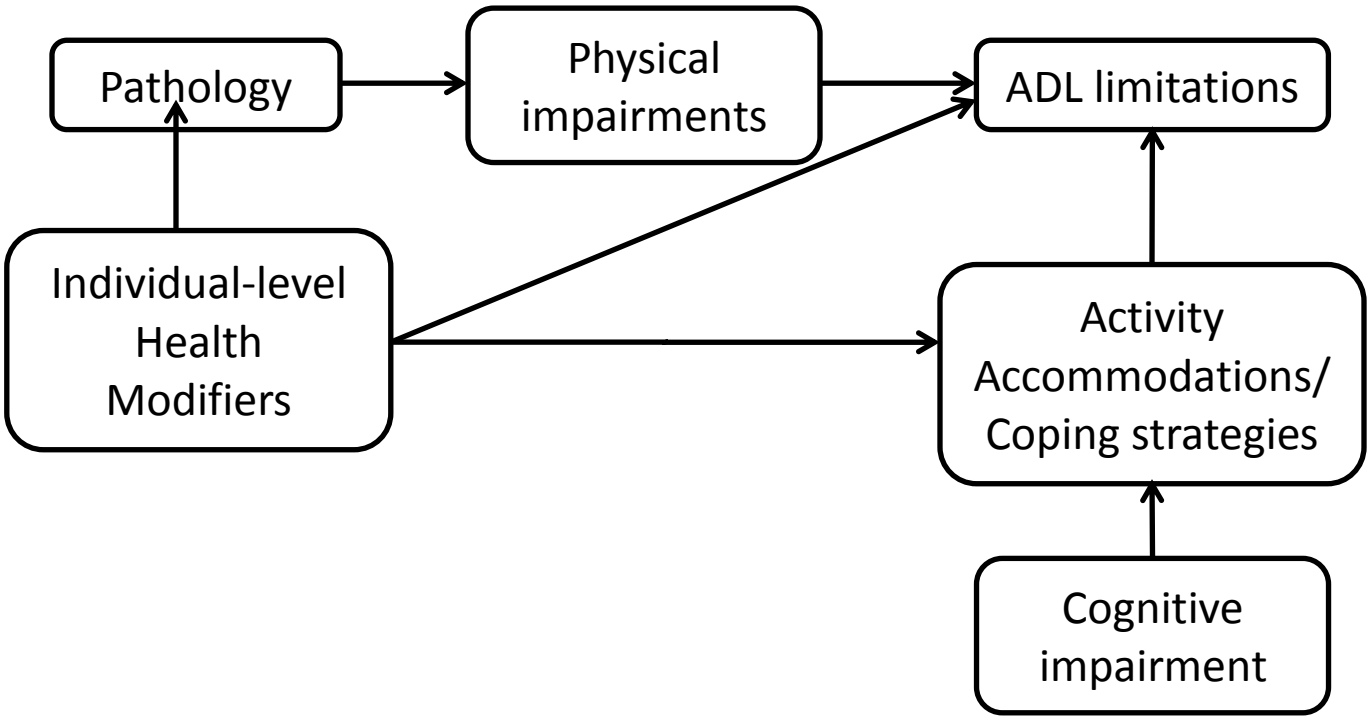
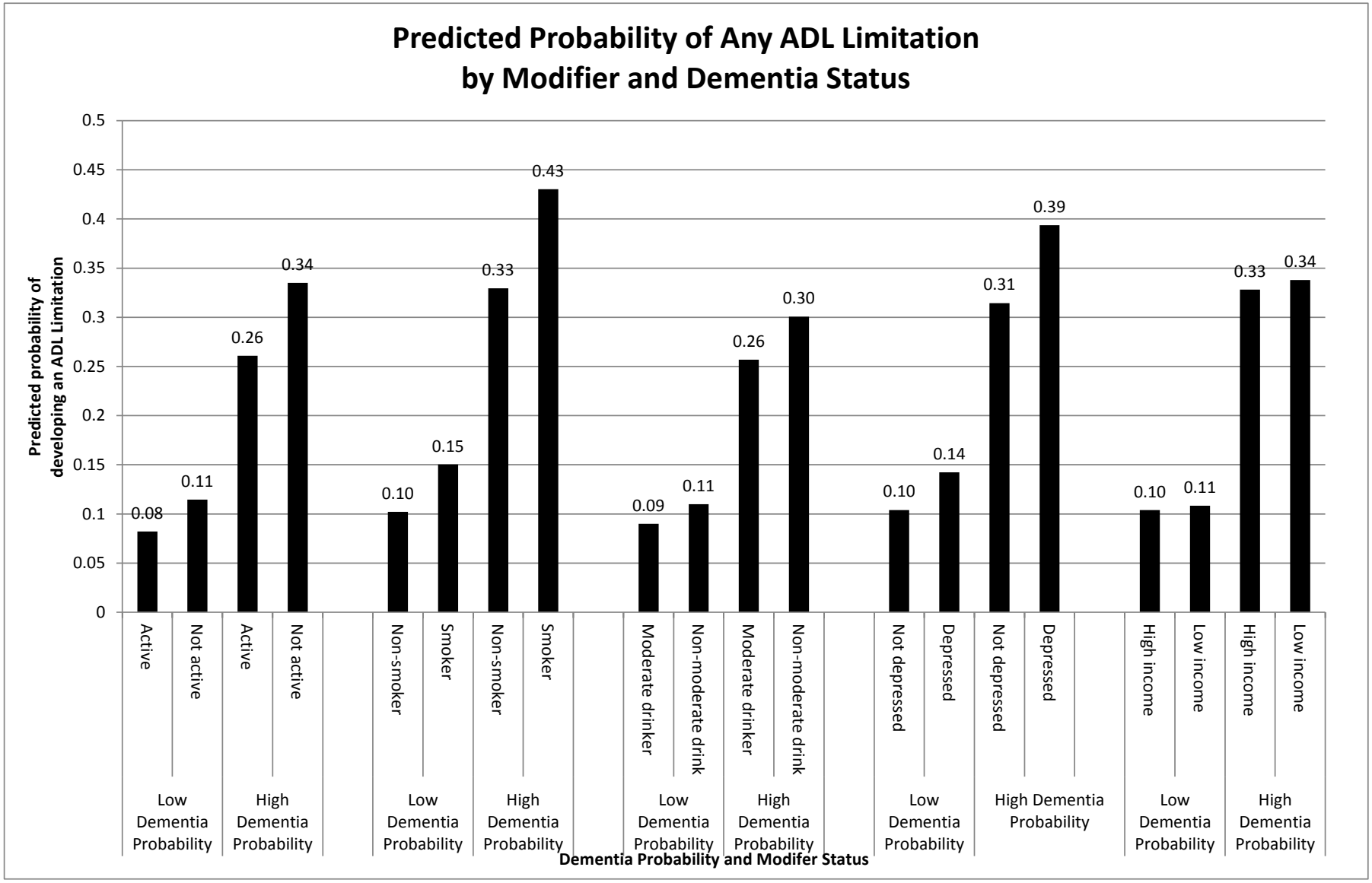
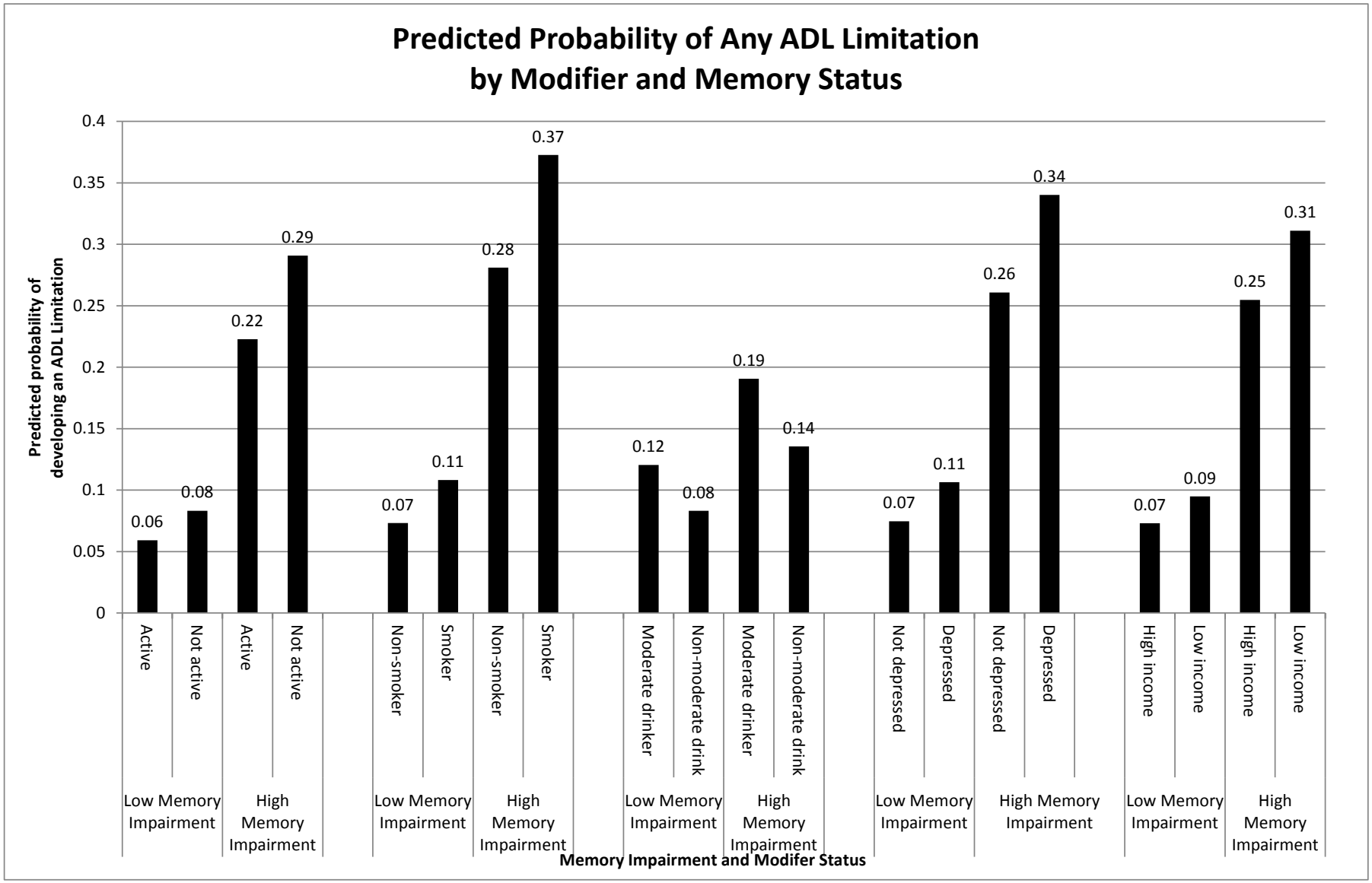


Figure 2. Predicted probability of any ADL limitation by modifier and dementia status.



Brief Explanation of Figure 2: Estimated marginal probabilities of developing any ADL limitation for each combination of risk factor status and high or low dementia probability category. This information is similar to that shown in Table 3, but instead of showing odds ratios (a relative measure of effect), this Figure shows the absolute probability of developing an activity limitation. For example, the estimated effect of physical activity on individuals with low dementia risk (comparing the 1st to the 2nd columns) is somewhat smaller than the absolute effect of physical activity on individuals with high demenita risk (estimated by comparing the 3rd to the 4th columns). We observe that the physical activity, not smoking and not being depressed appear to result in a greater decrease in the risk of developing an activity limitations among those who have high dementia probability compared to those who have low dementia probability.

Figure 3. Predicted probability of any ADL limitation by modifier and memory status.



Brief Explanation of Figure 3: Estimated marginal probabilities of developing any ADL limitation for each combination of risk factor status and high or low dementia probability category. This information is similar to that shown in Table 3, but instead of showing odds ratios (a relative measure of effect), this Figure shows the absolute probability of developing an activity limitation. For example, the estimated effect of physical activity on individuals with low dementia risk (comparing the 1st to the 2nd columns) is somewhat smaller than the absolute effect of physical activity on individuals with high demenita risk (estimated by comparing the 3rd to the 4th columns). We observe that the physical activity, not smoking and not being depressed appear to result in a greater decrease in the risk of developing an activity limitations among those who have high dementia probability compared to those who have low dementia probability.